Proportion and Factors Associated with Zinc Deficiency in Acute Diarrhea Patients

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ABSTRACT

Background: *Zinc may affect the intestinal immune response. No data has been available on zinc deficiency in adult patients with diarrhea, especially for Indonesian population. Zinc metabolism, etiologies, pathogenesis and clinical course of diarrhea may have various effects on zinc concentration in different population. This study aimed to determine the proportion of zinc deficiency in patients with acute diarrhea, including its associated factors.*

Method: *A cross-sectional study was conducted in patients with acute diarrhea at outpatient clinics and emergency wards of four hospitals between August 2010 and March 2011. A serum zinc concentration of < 10.7 µmol/L was set as cut-off value for zinc deficiency. Data was analyzed by using Chi-square test.*

Results: *There were 101 subjects, 54.5% were female, the median age was 26 years, median duration of acute diarrhea was 5 days, and the median frequency was 6 times/day. About 95% patients had nutritional status of subjective global assessment (SGA) A and the mean value of body mass index was 19.3 ± 0.70 kg/m^2. Approximately 88.1% patients had severe infective diarrhea based on hydration status. About 69.3% patients were zinc deficient with the mean serum zinc concentration of 9.26 ± 2.95 µmol/L. We found a significant correlation between the severity of diarrhea and zinc deficiency in patients with acute diarrhea.*

Conclusion: *The proportion of zinc deficiency in acute diarrhea patients was quite large although the mean serum zinc level was still below the National Health and Nutrition Examination Survey (NHANES) reference value. The severity of diarrhea has been proven to be significant that affects zinc deficiency in acute diarrhea patients.*

Keywords: *zinc deficiency, acute diarrhea, adult*

ABSTRAK

Latar belakang: *Seng diketahui dapat mempengaruhi respon kekebalan usus. Hingga saat ini belum ada data mengenai defisiensi seng pada kelompok pasien dewasa yang menderita diare khususnya di Indonesia. Adanya kebutuhan metabolisme seng, perbedaan faktor penyebab, patogenesis, dan perjalanan penyakit diare pada masing-masing populasi yang berbeda akan mempengaruhi konsentrasi seng. Penelitian ini bertujuan untuk mengetahui proporsi defisiensi seng pada pasien diare akut dan faktor yang berperan terhadap defisiensi seng pada pasien diare akut di rumah sakit.*

Metode: *Studi potong lintang dilakukan pada pasien diare akut yang berobat di poliklinik dan instalasi gawat darurat pada empat rumah sakit selama periode Agustus 2010-Maret 2011. Konsentrasi seng serum < 10,7 µmol/L merupakan nilai batas untuk menyatakan defisiensi seng. Analisis data dilakukan dengan uji kai kuadrat.*

Hasil: *Didapatkan sejumlah 101 pasien diare akut, 54,5% perempuan, usia rata-rata pasien 26 tahun, median lama menderita diare akut 5 hari dan median frekuensi diare per hari 6 kali. Status nutrisi 95% pasien termasuk subjective global assessment (SGA) A dengan rerata nilai indeks masa tubuh sebesar 19,3 ± 0,70 kg/m². Sebanyak 88,1% pasien menderita diare infektif yang berdasarkan status hidrasi tergolong dalam diare berat. Sebanyak 69,3% pasien mengalami defisiensi seng dengan rerata kadar seng serum 9,26 ± 2,95 umol/L. Terdapat hubungan bermakna antara beratnya diare berdasarkan status hidrasi terhadap defisiensi seng pada pasien diare akut.*

Kesimpulan: *Proporsi defisiensi seng pada pasien diare akut cukup besar dengan rerata kadar seng serum yang masih di bawah nilai referensi the National Health and Nutrition Examination Survey (NHANES). Faktor beratnya diare berdasarkan status hidrasi terbukti bermakna mempengaruhi defisiensi seng pada pasien diare akut.*

Kata kunci: *defisiensi seng, diare akut, dewasa*

INTRODUCTION

The incidence of diarrhea in developing countries is still high. Diarrhea affects 1 billion people worldwide each year and causes 1.54 to 2 millions death. In developing countries, it may reach greater number up to three fold. In Indonesia, the case fatality rate of diarrhea ranges between 1 and 2.5%. Most cases are acute diarrhea. The host is one of determining factors of morbidity and mortality associated with diarrhea. Of all conditions related to the host factor, nutritional status is the main factor affecting morbidity and mortality risk associated with diarrhea.[1-7] Diarrhea and malnutrition often occur together, particularly in developing countries. In this case, zinc micronutrient is one of factors related to the nutritional status.[1,4,8-16] Zinc deficiency is one of micronutrient malnutrition problems frequently found in patients who have treatment in the hospital. The risk of deficiency may be aggravated by diarrhea; while on the other hand, the zinc loss during diarrhea, either mild or severe, may affect the duration and severity of diarrhea. Both conditions produce a viscious cycle (diarrhea zinc deficiency diarrhea).[10,13,17-24]

Some changes are found in diarrhea with zinc deficiency including intestinal morphological changes (villous atrophy, reduced brush-border activity and altered intestinal permeability) and impaired immune function (such as lymphoid tissue atrophy, reduction in lymphocyte count and T helper cell proportion, cytotoxic activity of lymphocytes and natural killer cell activity).[20,25-29] Based on some clinical trials which have provided evidences on the effectiveness of zinc, concluded that there are some possible mechanisms regarding beneficial effects of zinc on the duration of diarrhea, i.e: (1) accelerating the regeneration of intestinal epithelial lining; (2) improving water and electrolyte absorption in the intestines; (3) increasing the enzyme levels of enterocyte brush-border; and (4) enhancing immune response that may promote clearance of pathogens from the intestines.[30-37]

Until now, there has been lack of studies on zinc status in Indonesian population. Furthermore, no study has been conducted to explore the zinc status in adult patients who had suffered from diarrhea. There is limited national data on zinc deficiency and further data on the prevalence of zinc deficiency is necessary, especially the subclinical deficiency in another age group. Knowledge on nutritional status and zinc concentration in adult patients who had diarrhea is extremely important. This study aimed to evaluate the proportion of zinc deficiency and factors related to the incidence of zinc deficiency in patients with diarrhea.

METHOD

This study was a cross-sectional study. It was conducted in adult patients with acute diarrhea who had their treatment at the outpatient clinics and emergency wards of four teaching hospitals, i.e. Cipto Mangunkusumo, Persahabatan, Tangerang, and Fatmawati Hospitals between August 2010 and March 2011. The inclusion criteria were patients who were older than 18 years and had suffered from diarrhea; while the exclusion criteria were patients who had taken supplementation of vitamin and micronutrients, steroid, anti-metabolite agents such as methotrexate, immunosuppressants and anti-tumor agents; patients who had suffered from liver cirrhosis, end-stage chronic renal disease, HIV/AIDS, alcoholism and burn injuries. The minimal sample size for this study was 100 patients. Explanation about the study was given to the eligible subjects and they gave their consent to participate in the study by signing the informed consent form. Subsequently, some examinations were performed including history taking, physical

examination, anthropometry, nutritional status assessment using subjective global assessment (SGA), laboratory investigation and fecal analysis.

Data was managed and analyzed using computer software, i.e. SPSS for windows version 17.0. Categorical data was analyzed descriptively for categorical variables. Results were presented in the text, table or graphics in the form of frequency and proportion. Numerical data was analyzed descriptively and presented as mean value and standard deviation for data with normal distribution and as median value and minimum-maximum range for data with abnormal distribution. Bivariate analysis was performed using Chi-square or fisher exact test. When we found two or more independent variables that had significant correlation with dependent variables, multivariate analysis was performed using logistic regression.

RESULTS

This study found a total number of 101 patients with acute diarrhea, which was consistent with expectation of the sample size. Patient characteristics are presented in Table 1 and 2.

Table 1. Baseline patient characteristics

	n	%
Age (years)		
18-25	46	45.5
26-35	46	45.5
> 35	9	8.9
Sex		
Male	46	45.5
Female	55	54.5
Education level		
Illiterate/no-schooling	2	2.0
Elementary school	1	1.0
Junior high school	27	26.7
Senior high school	66	65.3
University	5	5.0
Treatment		
No treatment	3	3.0
Personalized drug consumption	48	47.5
• Oral rehidration solutions	0	0.0
• Symptomatic drugs	18	37.5
• Antibiotic	6	12.5
• Combined drugs (symptomatic + antibiotics)	24	50.0
Clinic/primary health care visits	50	49.5
Subjective global assesment (SGA)		
SGA A	96	95.0
SGA B	5	5.0
SGA C	0	0.0
Body mass index (kg/m^2)		
< 18.5	0	0.0
18.5-22.9	101	100.0
≥ 23	0	0.0
Nutritional status		
Normal	96	95.0
Malnutrition	5	5.0
Etiology of diarrhea		
Infective	89	88.1
Non-infective	12	11.9
Severity of diarrhea		
Mild-moderate	32	31.7
Severe	69	68.3

Table 2. Distribution of patient characteristics based on mean value, median, standard deviation and minimum-maximum range

Characteristic	Mean	Median	SD	Range	
				Min	Max
Age (years)*		26.0		18.0	53.0
Body mass index	19.36		0.70		
Duration of diarrhea (day)*		5.0		1.0	10.0
Frequency of diarrhea (times/day)*		6.0		3.0	15.0
Daldiyono score*		3.0		0.0	5.0
Serum zinc concentration (µmol/L)	9.26		2.95		

*Abnormal distribution; SD: standard deviation

The standard value for zinc deficiency was consistent with The National Health and Nutrition Examination Survey United States of America (NHANES) reference value, which categorized zinc concentration of < 10.7 µmol/L.[38] The proportion of zinc deficiency could be seen in Table 3. Table 4 and 5 demonstrate that the severity of diarrhea is a significant factor that affects zinc deficiency in patients.

Table 3. Proportion of zinc deficiency in acute diarrhea patients

	n	%
Zinc deficiency	70	69.3
Normal	31	30.7

Table 4. Factors affecting zinc deficiency in patients with diarrhea

Characteristic	Mean	Median	SD	Range	
				Min	Max
Age (years)*		2 6.0		18.0	53.0
Body mass index	19.36		0.70		
Duration of diarrhea (day)*		5.0		1.0	10.0
Frequency of diarrhea (times/day)*		6.0		3.0	15.0
Daldiyono score*		3.0		0.0	5.0
Serum zinc concentration (µmol/L)	9.26		2.95		

Chi-square test; *fisher exact test; SD: standard deviation

Table 5. Multivariate tables for factors affecting zinc deficiency in diarrhea patients

Initial model of multivariate (logistic regression)

Variable	OR (CI 95%)	p
Etiology of diarrhea	4.59 (0.11-185.31)	0.419
Severity of diarrhea	902.62 (76.90-1060.40)	< 0.0001

Final model of logistic regression

Variable	B	Wald	OR (CI 95%)	p
Diarrhea severity	6.928	31.001	1020.00 (89.03-1169.0)	< 0.0001

Although the statistical analysis demonstrated that nutritional factors and etiologies of diarrhea did not have significant correlation with zinc deficiency in diarrhea patients, but when it was analyzed further, we found that there was lower median value on zinc concentration in patients who had malnutrition and suffered from infective diarrhea (Table 6) and the mean value of zinc concentration was consecutively lower with the increasing frequency and duration of diarrhea.

Table 6. Differences of median value on zinc concentration and affecting factors of zinc deficiency in patients with diarrhea

Affecting factors	Median value of zinc serum concentration (µmol/L)
Nutritional status	
Normal	9.07 (3.79-16.45)
Malnutrition	7.54 (6.14-13.40)
Etiology of diarrhea	
Non-infective	12.74 (6.04-16.45)
Infective	8.57 (3.79-15.19)
Severity of diarrhea	
Mild-moderate	12.09 (10.40-16.45)
Severe	7.83 (3.79-10.71)

DISCUSSION

The majority of patients in this study were female (54.5%) with median age of 26 years (range 18-53 years old). According to literatures, two-third of adult patients who suffered from acute diarrhea are at 21-40 years of age and some studies found greater number of incidence in female than male subjects.[31,39-42]

The education level of most respondents was high-school level (65.3%). However, the literatures indicate that acute diarrhea in developing countries often occur at the low socio-economic level and low education level.[43] Different results may be found since this study was conducted at referral hospitals; thus there was indirect shift of demographic characteristic to middle class of educational level that had good awareness to seek further treatment.

No patient was categorized into malnutrition based on body mass index (BMI) classification with mean value of BMI of 19.36 kg/m^2 (SD ± 0.70 kg/m^2). However, when SGA classification was used, there were 5 patients who were categorized into SGA B. Such condition may occur because in the SGA assessment, altered body weight, changes in dietary intake and gastrointestinal symptoms are also taken into consideration. This study finding is different from the study conduncted by Strand et al, that demonstrated only 46% respondent with good nutritional status.[42] The different results between this study and previous study are due to different subject characteristics. The study by Strand et al, evaluated children and in such age group, malnutrition is one of condition often found in patients with diarrhea.[42] Moreover, most of subjects in this study had high-school educational level (65.3%) who had better information, knowledge and needs on nutrition compared to the children group that highly dependent on their care givers.

In this study, most of cases were caused by infective diarrhea. Such result is consistent with the literarture mentioning that the major etiology of acute diarrhea in adult patients is due to infection.[41,43-45] It is also supported by Setiawan et al, concluded that the etiology of acute diarrhea in adult patients is mostly bacterial infection.[45] The study results are also similar to some study results of diarrhea in children of developing countries, which indicated that diarrhea is caused by infection and malnutrition may appear as the most often comorbitiy and aggrevating factor. However, there are some differences between both groups, i.e. infective diarrhea in children is mostly caused by virus and the mechanism of zinc loss is based on pathophysiology of osmotic and secretoric diarrhea;

while infective diarrhea in adult patients is mostly caused by bacterial infection and the zinc loss is mainly based on pathophysiology of inflammatory diarrhea.[45]

At present, there is no standard definition and reference value for zinc deficiency. Most studies categorize zinc deficiency when the zinc concentration is < 10.7 µmol/L based on reference value issued by NHANES. In this study, zinc deficiency was defined when the serum zinc concentration was < 10.7 µmol/L; thus we found 69.3% of patients who had zinc deficiency with mean zinc concentration of 9.26 µmol/L (SD ± 2.95 µmol/L). The result is similar with previous studies that were conducted in children population.[35,36,46]

Zinc deficiency in patients who had acute diarrhea in Indonesia is lower when compared to other countries. It may be associated with age, nutritional status, severity of illness, duration and frequency of diarrhea. It could be concluded by considering various overseas studies on diarrhea involving children, which demonstrate that most respondents had more severe malnutrition and longer duration and more frequent diarrhea.[33-39] The serum zinc concentration is naturally lower in the childhood and it increases during teenager and early adolescence and decreases with age. Zinc deficiency is associated with five general etiologies, such as inadequate intake, increasing needs, malabsorption, increasing loss and impaired utilization. Basically, zinc deficiency occurs when the absorbed zinc intake is inadequate.

Mean zinc concentration of acute diarrhea patients in this study was 9.26 µmol/L. The mean value is lower than the mean serum zinc concentration of healthy subjects in a study conducted by Putranti, which evaluated junior-high teenagers in Semarang with serum zinc concentration of 19.83 µmol/L.[47] The mean value of serum zinc concentration of this study is also lower compared to the study conducted by Anisa which evaluated pneumonia patient, i.e. 16.43 µmol/L.[48] Compared to the patients characteristics in the study by Anisa, this study revealed subject characteristics of younger age and better nutritional status. Moreover, there was also different comorbidity. This study was conducted in patients with diarrhea, that may cause increased zinc loss through the intestines resulting in lower zinc concentration. The mean zinc concentration of this study is also lower than serum zinc concentration in normal subjects as found by Prasad et al in Detroit revealing mean serum zinc concentration of 15.51 µmol/L in 18-54 years age group.[49]

Comparing to another study on zinc deficiency in Indonesia, a study by Yustina, in female teenager in Tangerang revealed a range of serum zinc concentration of 11.9 ± 2.2 µmol/L.[50] The result was higher than this study finding despite the respondents had lower macronutrient and micronutrient intake of their daily consumption; while 95% respondents of this study were categorized into SGA A. The rational for such condition is this study was conducted in patients with diarrhea that may cause increased zinc loss through intestinal routes and resulting in lower zinc concentration.

A study conducted by Lind et al, which was also performed in Indonesia in children with 6.1 ± 0.4 months of age demonstrated serum zinc concentration of 9.24 ± 2.14 µmol/L. Such result was similar to this study finding which found serum zinc concentration of 9.26 ± 2.95 µmol/L.[51]

A study conducted by Strand et al, revealed the proportion of zinc deficiency, mean serum zinc concentration in acute diarrhea patients, as well as factors associated with zinc deficiency. The study also identified that nutritional status, infective diarrhea and hydration status are correlated to low plasma zinc concentration.[42]

In this study, half of patients had suffered from zinc deficiency (69.3%) although most of them had normal nutritional status (95%). In spite of good nutritional status in most respondents, the zinc concentrations both in malnutrition and normal nutrition group were still below the NHANES reference value. In this study, the malnutrition group had lower zinc concentration than the group with normal nutritional status. On further analysis, it is obvious that there is no correlation between nutritional status and zinc deficiency. It is due to most of respondents have normal nutritional status.

Most respondents had infective diarrhea and we could observe that the zinc concentration in the infective diarrhea group was lower than the non-infective diarrhea group. This fact is consistent with the study conducted by Strand et al explaining that lower zinc concentration in infective diarrhea is due to more severe inflammatory process.[42,52] Bivariate analysis showed that there was a correlation between the etiology of diarrhea and zinc deficiency. However, the analysis also indicated that the etiology of diarrhea did not affect the incidence of zinc deficiency. It may occur because most respondents suffered from infective diarrhea (88.1%).

The majority of patients were categorized into severe dehydration. It may be found since most respondents were having treatment at the emergency wards and outpatient clinics. It is also obvious that the longer duration and the more frequent diarrhea

suffered by the patients, the lower serum zinc concentration would be found. Further analysis revealed that the severity of diarrhea based on dehydration stage is associated with zinc deficiency.

After statistical test had been performed, it is identified that the severity of diarrhea based on dehydration stages was the only variable that significantly proven to affect zinc deficiency in diarrhea patients. However, the result of such analysis should be evaluated further since the proportion of zinc deficiency is greater than the non-deficiency group. In the group with zinc deficiency, there is imbalance on distribution of proportion and there are values on < 5 cells.

Although the variables of nutritional status and etiology of diarrhea were not statistically significant in affecting zinc deficiency, but the results of this study demonstrated that there are more malnutrition patients who had zinc deficiency compared to patients with normal nutrition. Zinc deficiency is also more frequent in acute diarrhea patients with infective diarrhea compared to the non-infective cause of diarrhea (75% vs 25%).

When it was analyzed further by comparing the median value of zinc concentration and factors affecting zinc deficiency, it was found that there were consecutively lower zinc concentration in patients who suffered from malnutrition, had infective diarrhea, and who had diarrhea with more severe dehydration.

Another fact that should be noticed, until now, there has been no study and consensus on the cut off value for zinc deficiency, especially for adult population in Indonesia. The cut off point of 10.7 μmol/L that had been used in this study is based on the study results conducted by NHANES.

In this study, the history taking, physical examination and laboratory investigation were only performed once; therefore, it could not provide any explanation on the dynamics of altered zinc concentration of certain period of time. The study design also does not allow us to determine the correlation of causal and effect. This study also did not calculate the dietary zinc intake. The determination of zinc status was based on serum zinc concentration without involving any control due to limitation of research fund. No measurement was performed on zinc excretion in the stool. Evaluation on etiology of diarrhea also did not involve stool culture to reveal definitive causes.

CONCLUSION

The proportion of zinc deficiency in adult patients who suffered from acute diarrhea is quite large with the mean serum zinc concentration which is still below the NHANES reference value. The severity of diarrhea based on hydration status has been proven to be significant that affects zinc deficiency in acute diarrhea patients.

SUGGESTION

Considering the extremely high proportion of zinc deficiency in adult patients with acute diarrhea, it is important to pay attention on serum zinc concentration in patients with acute diarrhea. Knowledge and skills on the importance of rehydration should be socialized at the primary health care services. Further studies with clinical trial designs are necessary to explore the role of zinc in chronic diarrhea and the advantage of zinc supplementation to improve the severity of diarrhea.

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